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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,625	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendment filed August 24, 2006 is acknowledged and has been entered. Claims 1-18 have been canceled. Claims 19-39 are now pending in the present application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The information disclosure statement filed December 22, 2003 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Copies of references that were available to the Examiner have been considered and initialed on the attached Form 1449. The Examiner has not considered references that were not available. If Applicants desire all references to be considered, a copy should be provided in response to this Office Action.

References found in application 09/818918 have been considered. References found in 08/738652 (now US Patent 6207646) are not readily available to the Examiner. Currently, this application (08/738652) is at the Board of interferences.

In the ***January 9, 2006*** amendment, Applicants have stated that in "...order to advance prosecution Applicants will submit the requested references and a new form 1449. Applicants respectively request that the Examiner consider each of the

references and return an initialed copy of the 1449 to Applicants. The Examiner will consider any and all references provided by Applicants.

In the ***August 24, 2006*** amendment, Applicants have stated, "...a list of co-pending applications and the references cited in Application No. 08/738,652 will be submitted. Applicants respectively request that the Examiner consider each of the references and return an initialed copy of the 1449 to Applicants." (Remarks, p. 2) As of November 25, 2006 "a list of co-pending applications and the references cited in Application No. 08/738,652..." has not yet been filed with the USPTO.

4. Claims 19-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-49 of U.S. Patent No. 6239116. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the application and patent have claims directed to method of administering an immunostimulatory oligonucleotide to a subject. The claims of the application recite that the method is for treating asthma and the patent claims recite the method is for inducing IL-6 in a subject. Treatment of asthma by administering the immunostimulatory oligonucleotide induces a Th1 immune response, which includes inducing the cytokine IL-6. It would be obvious that the recited steps in the methods claim would achieve both results, treatment of asthma and inducing IL-6.

This rejection is maintained for the reasons of record. In the August 24, 2006 amendment Applicants have asserted that the preamble to claim 19 specifies that the claim is a method of treating asthma and that it is not possible to treat asthma on a subject that does not have asthma. Applicants have also asserted that

it would be clear to one of ordinary skill in the art that claim 19 and its dependent claims necessarily relates to a subject that has asthma. However, 6239116 does teach stimulating immune activation by administering the nucleic acid sequences of the invention to a subject and that the immune activation effect is predominantly a Th1 pattern of immune activation (col. 6). Further, 6239116 teaches redirecting a subject's immune response from Th2 to Th1 and that this can be used to treat an asthmatic disorder (col. 7). Inducing IL-6 in a subject is indicative of a predominantly Th1 pattern of immune activation.

5. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102 and 103 of copending Application No. 09/337584. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method for treating asthma in a subject, comprising administering to the subject an effective amount for treating asthma in the subject of an immunostimulatory oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46, 52, 64, 71, 72, 74 and 80 of copending Application No. 10/613739. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method comprising

administering to the subject an immunostimulatory oligonucleotide. Although 10/613739 does not recite treatment for asthma, this would be the result since the methods steps are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 23, 31, 32 and 34-37 of copending Application No. 10/769282. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method comprising administering to the subject an immunostimulatory oligonucleotide. Although 10/769282 does not recite treatment for asthma, this would be the result since the methods steps are the same. Application 10/769282 recites a method of modulating an immune response, the administration of the immunostimulatory oligonucleotide modulates a Th1 immune response, which is the immune response modulated in an asthmatic subject that has received the immunostimulatory oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-29 and 31-33 of copending Application No. 10/894862. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method comprising administering to the

subject an immunostimulatory oligonucleotide. Although 10/894862 does not recite treatment for asthma, this would be the result since the methods steps are the same. Application 10/894862 recites a method of inducing a Th1 immune response and suppressing a Th2 immune response, the administration of the immunostimulatory oligonucleotide modulates a Th1 immune response, which is the immune response modulated in a asthmatic subject that has received the immunostimulatory oligonucleotide; the Th2 immune response is suppressed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 42, 45-53, 57-60 of copending Application No. 09/337893. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims directed to a method comprising administering to the subject an immunostimulatory oligonucleotide. Although 09/337893 does not recite treatment for asthma, this would be the result since the methods steps are the same. Application 09/337893 recites a method for redirecting a subject's immune response from a Th2 to a Th1 immune response, the administration of the immunostimulatory oligonucleotide modulates a Th1 immune response, which is the immune response modulated in an asthmatic subject that has received the immunostimulatory oligonucleotide; the Th2 immune response is suppressed.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. The provisional obviousness-type double patenting rejection over 09/337584, 10/613739, 10/769282, 10/894862 and 0/337893 is maintained. Applicants' arguments filed August 24, 2006 have been fully considered but they are not persuasive. Applicants have asserted that the rejections are provisional since none of the claims in the 09/337584,10/613739, 10/769282, 10/894862 and 0/337893 applications have been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

11. Claims 19-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating asthma in a subject (murine model), comprising administering to a subject an immunostimulatory oligonucleotide (CpG, specifically SEQ ID NO: 10), does not reasonably provide enablement for a method for treating asthma in a subject (animal or human), comprising administering to a subject (animal or human) an immunostimulatory oligonucleotide (CpG, the scope of the myriad possible immunostimulatory oligonucleotides encompassed by the claims). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for treating asthma comprising: administering to a subject (human, dog, cat, horse, and cow) an immuno-stimulatory oligonucleotide comprising an immunostimulatory motif comprising a 5'-cytosine-guanine-3','wherein the immunostimulatory oligonucleotide is administered without an allergen in an amount effective to treat asthma. The

claims define various immunostimulatory oligonucleotides as well as encompassing numerous immunostimulatory oligonucleotides (CpG oligo-nucleotide formulas are 5'$X_1X_2CGX_3X_4$ 3', wherein X_1, X_2, X_3, and X_4 are any nucleotide; X_1CGX_2, wherein X_1 is G and A and X_2 is T and C). The claims define various routes of administration and delivery formulations.

It is noted that the specification teaches that the mechanism of immune response in the treatment of asthma is a redirecting of the subject's immune response from a Th2 to a Th1 immune response. The specification teaches that certain nucleic acids containing unmethylated CpG dinucleotides activate lymphocytes in a subject and redirect a subject's immune response from a Th2 to a Th1 (e.g. by inducing monocytic cells and other cells to produce Th1 cytokines, including IL-12, interferon gamma and GM-CSF) (see pp. 7-8). "In addition, the nucleic acid sequences can be administered to stimulate a subject's response to a vaccine. Further, by redirecting a subject's immune response from Th2 to Thl, the instant claimed nucleic acid molecules can be administered to treat or prevent the symptoms of asthma. In addition, the instant claimed nucleic acid molecules can be administered in conjunction with a particular allergen to a subject as a type of desensitization therapy to treat or prevent the occurrence of an allergic reaction." (p. 8, l. 11-15) The specification defines asthma as well as allergy and allergens (see p. 12).

Example 12 of the specification (pp. 52-53) teaches a murine model of asthma. Mice were immunized SEA to induce a Th2 immune response (e.g. production of IgE antibody). IgE antibody production is known to an important cause of asthma. The immunized mice were then treated with oligonucleotides; SEQ ID NO: 10 was the experimental immunostimulatory oligonucleotide and

SEQ ID NO: 11 was the control oligonucleotide. Mice were sacrificed and whole lung lavage was performed to harvest airway and alveolar inflammatory cells. Cytokine levels were measured, RNA was isolated for northern blots and a histological examination of lungs was performed.

SEQ ID NO: 10 (TCCATGACGTTCCTGACGTT), at low doses, can give protection (figure 12). Suppression of eosinophilic inflammation was associated with a suppression of a Th2 response and induction of a Thl response; cytokines that increase in relation to a Th1 immune response include interferon-gamma, TNF-beta and IL-12. Figure 15 shows that administration of an oligonucleotide can redirect the cytokine response of the lung to production of IFN-gamma, indicating a Th1 type of immune response. The specification indicates that Figures 9-15 show that CpG/SEA induced inflammatory cells, eosinophils, to be present and generated macrophages; higher IL-12 was induced, IL-4 was reduced and IFN-gamma production increased.

The specification does not teach that any of the other myriad of possibilities of CpG having the claimed formulas can be used to treat an asthmatic subject (redirecting a Th2 to Th1 immune response), animal or human.

The state of the art is unpredictable with regard to asthma treatments using CpG. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms. Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (see McCluskie et al Molecular Med., 1999, 5/5:287-300 in its entirety, and especially on p. 296; see Krieg et al, Immunology Today, 2000, 21/10:521-526, especially p. 524). Wohlleben et al 2001 (TRENDS in Immunology, 2001, 22/11:618-626) have

studied the effects of CpG on atopic disorders such as allergic asthma. CpG-ODNs have multiple stimulatory effects on lymphocytes, including DCs, macrophages, B cells, natural killer (NK) cells and T cells (p. 619). The state of the art questions whether "CpG-ODNs can be used in humans to inhibit the development of asthma? In vitro experiments have shown clearly that human cells react to CpG-DNA in a similar manner to lymphocytes from rodents.... The results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders. However, treatments using CpG-ODNs rely both on innate and adaptive pro-inflammatory Th1 immune responses to inhibit Th2 responses. For this reason, harmful side-effects of the treatment need to be ruled out. Besides potential problem of inducing strong inflammatory responses at the site of exposure to allergen, the use of CpG-DNA could also have other serious side-effects. It has been reported that the application of CpG-ODNs can cause septic shock in mice. A further potential problem might be the development of autoimmune disease after application of CpG-DNA. Residual autoreactive T cells might become sufficiently activated to cause disease after encountering APCs that have been unspecifically activated by CpG-DNA." (p. 620, col. 2) Wohlleben et al teaches that all approaches that induce Th1 responses have the potential side-effects of Th1-cell-mediated inflammation, potentially causing serious tissue damage (p. 624, col. 1). Kline et al 2002 (Am. J. Physiol. Lung Cell Mol. Physiol., 2002, 283:L170-L179; Kline et al, J. Immunol. 1998, 160:2555-2559) teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model (p. L172, col. 2; see also p. L178, paragraph bridging cols. 1-2). Kline et al 2002 teaches that splenocytes from OVA-treated mice did not develop an antigen-

specific Th1 phenotype. However, mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2).

Weiner (J. Leukocyte Biology, 2000, 68:456-463) states furthermore that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (see p. 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agrawal et al Molecular Med. Today, 2000, 6:72-81, especially on pp. 78-80).

Further, Satoh et al (Fukushima Igaku Zasshi, 2002, 52/3:237-250, abstract only) teaches that CpG-ODN is responsible for worsening of allergic contact dermatitis. "S.c. applied CpG ODN one day before sensitization of naïve mice significantly enhanced the ACD to DNFB which showed severe edema with massive CD8+ T cell infiltration." (abstract) Satoh et al also teaches that "[T]hese results indicate that CpG ODN vaccinations may elicit and aggravate side effects such as harmful CD8+ T cell-mediated type IV hypersensitivity responses." (abstract) Dziadzio et al (Handbook of Experimental Pharmacology, 2004, 161(Pharmacology and Therapeutics of Asthma and COPD):273-285, abstract only) teaches that "[V]arious combinations of plasmid DNA, immunostimulatory oligonucleotide (ISS-ODN), and proteins have been studied in murine models to evaluate the effectiveness of DNA vaccination. The success in skewing the immune response towards a Th1 phenotype in mice still needs to be evaluated in humans. The use of DNA vaccination as a treatment for allergic disease remains a

viable option for the future." (abstract) Barnes (European J. Internal Medicine, 2000, 11:9-20) teaches that immunostimulatory oligonucleotides are potent inducers of Th1 cytokines and in mice, administration of CpG-ODN increases the ration of Th1 to Th2 cells, decreases formation of specific IgE and reduces the eosinophilic response of allergen (p. 17). Barnes teaches that the animal studies encourage the possibility that vaccination might prevent or cure atopic disease in the future (p. 17; see also Hussain et al, J. Invest. Dermatol. Symp. Proc., 2004, 9:23-28; Serebrisky et al, J. Immunology, 2000, 165:5906-5912).

Further, Van Uden et al (J. Allergy Clin. Immnol., 1999, 104:902-910) teaches that although "ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN." (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2). Van Uden et al indicates that the ISS *may be a promising* method of treatment/prophylaxis for allergic disease, but that there are also some potential side effects that must be considered. The "immune system is delicately balanced between immunity and tolerance, between Th1 and Th2, and between inflammation and unresponsiveness. There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers." (p. 907, col. 2) LPS is similar to ISS, in view of this some of the same problems observed with LPS are potential problems with ISS (p. 907, col. 2). ISS could cause excessive

local inflammation as seen with other powerful Th1 adjuvants, such as CFA (p. 908, col. 1).

The state of the art, taken as a whole, is still unpredictable with regard to the use of an immunostimulatory oligonucleotide in treating asthma in a subject (human or otherwise) in need of such treatment. The state of the art several years after Applicants' effective filing date teaches that the methods claimed by Applicants are still not enabled and discusses the myriad problems related to immunostimulatory oligonucleotide and asthma treatments.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward a method for treating asthma in a subject comprising the administration of any immunostimulatory oligonucleotide comprising the formulas set forth in the claims. As previously stated the specification teaches an increase in immuno-modulation in mice (and comprising conversion from a Th2 to a Th1 immune response), and treatment of asthma in a mouse model comprising the administration of SEQ ID NO: 10. One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of asthma in any organism (pending claims recite human, dog, cat, horse and cow) comprising the administration by any route of any immunostimulatory nucleic acid comprising the formulas in the claims in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms/subjects. The specification as filed fails to provide particular guidance which resolves the known unpredictability in

the art associated with effects provided *in vivo* in any and/or all organisms upon administration via any route of CpG containing oligonucleotides, and further whereby treatment effects are provided in any and/or all organism for asthma, which is redirecting a subject's immune response from a Th2 to a TH1 immune response. The breadth of the claims is very broad and the quantity of experimentation required is undue. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms/subjects, and further whereby treatment effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment of asthma comprising administration by any route of any CpG containing oligonucleotide (claimed formulas), and since determination of these factors for a particular CpG containing oligonucleotide and for the particularly claimed conditions, route of administration and organism is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

The examples provided evidence of the induction of various interleukins in spleen, liver or thymus cells are not representative of the successful treatment of asthma, which is redirecting the subject's immune response from a Th2 to aTh1 immune response, using any CpG containing oligonucleotide. No correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response in vitro (e.g. amount of IL-6 induction) and their ability to treat asthma *in vivo*. An assumed common mechanism of action does not ensure enablement for treatment. Effective delivery to appropriate and

concentration of a particular CpG containing oligonucleotide necessary for providing treatment for asthma (i.e. redirection from Th2 to Th1 immune response in a subject) for a particular CpG containing sequence are still highly unpredictable. The success of redirecting a subject's immune response from a Th2 to a Th1 immune response with SEQ ID NO: 10 is not necessarily representative or correlative of the ability to successfully redirecting a subject's immune response from a Th2 to a Th1 immune response with any of the generic sequences claimed and the myriad possibilities of CpG sequences encompassed by the claims. The *in vivo* treatment success for these generic sequences require undue experimentation beyond that provided in the instant disclosure.

Finally, it should be noted that whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b).

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date.

35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used.

The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424

(CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).

In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled.

The examples provided of the induction of various interleukins in spleen, liver or thymus cells are not representative of the successful treatment of asthma

using any CpG containing oligonucleotide. No correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response in vitro (e.g. amount of IL-6 induction) and their ability to treat asthma *in vivo*. An assumed common mechanism of action does not ensure enablement for treatment. Effective delivery to appropriate and concentration of a particular CpG containing oligonucleotide necessary for providing treatment for asthma for a particular CpG containing sequence are still highly unpredictable. The success of treating asthma with SEQ ID NO: 10 is not necessarily representative or correlative of the ability to successfully treat asthma with *any* of the *generic sequences* claimed and the *myriad* possibilities of CpG sequences encompassed by the claims. The *in vivo* treatment success for these generic sequences would require undue experimentation beyond that provided in the instant disclosure.

The rejection is maintained for the reasons of record. Applicant's arguments filed January 9, 2006 have been fully considered but they are not persuasive. Applicants have asserted that the specification describes a class of molecules (oligonucleotides) having a common structural motif, CpG dinucleotide, that when administered to a subject results in the immune response being altered, with a Th1 response being favored. Applicants have asserted that the data in the application, such as Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. The specification describes this as well as presents data, in vivo and in vitro, using a number of different CpG containing oligonucleotides (see Table 5). The Examiner appreciates Applicants pointing out specific descriptions and data; however, does the *in vivo* data from one CpG molecule, SEQ ID NO: 10, indicate that all other CpG molecules will function in the same manner (i.e. increase the Th1 response, sufficient to treat a subject having asthma)? It appears that not all CpG molecules increase the Th1 response. Does SEQ ID NO: 35

increase the Th1 response? What is the minimum level of cytokine (IFN-gamma and IL-12) increase necessary to indicate that a Th1 response has occurred?

Applicants have asserted that "...data need not support that every CpG oligonucleotide work equivalently or even work at all. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 1984 (upholding district court decision that patent on emulsion formulations was valid even though it was, in the words of the defendant, a mere "list of candidate ingredients"), it was stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude...possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide would not work equivalently or that it is possible that some rare oligonucleotides might not work at all is not a sufficient basis for rejecting the claims." (p. 5 of 15) However, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Although, typically, inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In re Angstadt, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

Applicants have asserted that McCluskie et al is an article describing DNA vaccines against Hepatitis B virus. On page 296, the page identified by the examiner, the reference mentions that one of the factors involved in influencing the Th bias of the response to DNA vaccines is the presence of CpG motifs. The reference is not relevant to the enablement of the pending claims because the

pending claims do not encompass plasmid vectors (or DNA vaccines). The pending independent claims are directed to the use of oligonucleotides. The issues of predictability and therapeutic effectivity are very different for CpG oligo-nucleotides and DNA vaccines. However, the claims do not recite that any kind of protein added in the composition of the CpG immunostimulatory nucleic acid being administered; the claims do not specifically exclude plasmids, vectors or DNA vaccines. The immunostimulatory nucleic acid could read on the whole bacteria, or the immunostimulatory nucleic acid could be part of a DNA vaccine; the claims just recite an immunostimulatory oligonucleotide comprising.

Applicants have asserted that each of the references (Krieg et al 2000, Wohlleben et al 2001, Kline et al 2002, Kline et al 1998, Weiner et al 2000, Agrawal et al 2000, Satoh et al 2002, Dziadzio et al 2004 Barnes 2000 and Van Uden et al 1999) cited to show that the state of the art is unpredictable with regard to the claimed method actually shows promise, may be a promising, probable successful use in humans, potential and/or suggestion of the claimed invention and its enablement. It is noted that even though these references may suggest the possibility if CpG's usefulness in treating a subject having asthma, they still also indicate even several years after Applicants' effective filing date that the scope of the claimed method is not enabled.

Applicants have asserted that several Phase I and II studies have been performed in humans to date. In particular subcutaneous administration, like that in the Satoh reference, has been performed in humans for a cancer trial. Applicants have asserted that the data are described in Kim et al 2004 abstract. However, the pending claims are directed to treatments for asthma and allergies, not cancer.

Applicants have asserted that numerous working examples were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims. Consistent with the descriptions, a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. For instance, US Patent Application Serial No. 10/644,052 corresponding to PCT Publication No W02004/016805 (copy previously submitted) describes numerous examples of CpG oligonucleotides that stimulate an immune response. However, 10/644052 is evidence of enablement post filing; the specification must be enabled at the time of filing, particularly in view of the state of the art regarding the claimed invention. Further, were the experimental

protocols set forth in 10/644052, specifically Examples 22, 25 and 26, the same manner as the experimental protocols of the pending application?

The rejection is maintained for the reasons of record. Applicant's arguments filed August 24, 2006 have been fully considered but they are not persuasive and have been addressed previously. It is noted that with regard to Kim et al, that Applicants have asserted previously that the claims are not directed to safety and that safety is not a consideration when determining enablement of the claimed invention.

12. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is vague and indefinite in the recitation of "wherein inflammation is prevented". The claim is directed to treating asthma and that the immunostimulatory oligonucleotide is administered "in an amount effective to treat asthma". However, the specification states that "Asthma" - refers to a disorder of the respiratory system characterized by inflammation, narrowing of the airways and increased reactivity of the airways-to inhaled agents. Asthma is frequently, although not exclusively associated with atopic or allergic symptoms." (p. 12, l. 28-31). It is not clear how inflammation is prevented when the claims recite treating asthma and the specification indicates that asthma refers to a disorder of the respiratory system characterized by inflammation. How is the immunostimulatory oligonucleotide preventing inflammation if it has already occurred since the claim is directed to treating?

13. Claims 19-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims recite "...an immunostimulatory oligonucleotide comprising an immunostimulatory motif comprising a 5'-cytosine-guanine-3'...".

The claims do not define the structure of the immunostimulatory oligonucleotide comprising an immunostimulatory motif comprising a 5'-cytosine-guanine-3'. What is the exact structure of the immunostimulatory oligonucleotide? The claims only recite that it must contain a 5'-cytosine-guanine-3'. The structure is not defined.

The structure of the immunostimulatory oligonucleotide is vast in view of the recitation of the open claim language of "comprising". Further, it is noted that neither the specification nor the claims disclose the structure of the oligonucleotide set forth in the claims. The recitation of comprising indicates that there are other structural components to the claimed immunostimulatory oligonucleotides and these the structures of the additional nucleic acids in the immunostimulatory oligonucleotides are not known. The immunostimulatory oligonucleotides recited in the pending claimed genus would not clearly apprise one skilled in the art that the inventors had possession of the claimed genus and all species encompassed thereby as of the filing date. The structure of these immunostimulatory oligo-nucleotides has not been specifically defined. The claims do not set forth the specific structure of the claimed immunostimulatory oligonucleotides and it is not clear if the claims or specification give the structure and a function of the

immunostimulatory oligonucleotides, as required by the written description guidelines.

It is noted that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed.

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is

made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original); Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) ("the specification does not clearly disclose to the skilled artisan that the inventors ... considered the ratio... to be part of their invention .... There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion").

The claims are drawn to a vast genus of immunostimulatory oligonucleotides. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention

is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics

sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original). In Ex parte Ohshiro, 14 USPQ2d 1750 (Bd. Pat. App. & Inter. 1989), the Board affirmed the rejection under 35 U.S.C. 112, first paragraph, of claims to an internal combustion engine which recited "at least one of said piston and said cylinder (head) having a recessed channel." The Board held that the application, which disclosed a cylinder head with a recessed channel and a piston without a recessed channel did not specifically disclose the "species" of a channeled piston.

14. No claims are allowed.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
November 25, 2006